REMARKS

This document is submitted in response to the final Office Action mailed July, 7, 2005 ("Office Action").

Applicants have amended claim 8. Support for the amendment can be found in original claim 8 and in the Specification, e.g., at page 22, line 11 through page 23, line 3. No new matter has been introduced.

The amendment, made solely to more particularly point out and distinctly claim the subject matter of this invention, should be entered as it raises no new issue that will require further consideration or search and also does not touch the merits of the application within the meaning of 37 C.F.R. § 1.116(b).

Only claims 8 and 20 are currently being examined. Reconsideration of these claims is requested in view of the following remarks.

The Office Action rejects claims 8 and 20 under under 35 U.S.C. § 102(b) as anticipated by Edwards *et al.* ("Edwards"). See page 2, lines 11-12. Applicants respectfully traverse.

I

The Office Action alleges that Edwards discloses a pharmaceutical preparation containing proNGF as the active ingredient, albeit one that has little activity. See page 3, line 2; and page 4, lines 13-19.

Applicants respectfully submit that Edwards only describes converting pro-NGF to the active β-NGF protein by enzymatic cleavage. Indeed, according to Edwards, proNGF has little or no biological activity.

As currently amended, independent claim 8 covers a pharmaceutical preparation in which proNGF (1) is the active ingredient, and (2) has activity comparable to that of β-NGF. See the Specification, e.g., page 22, line 11 through page 23 line 3.

Edwards discloses only crude compositions containing proNGF, rather than pharmaceutical compositions containing proNGF. In Example 2, Edwards describes *in vitro* translation of mouse proNGF in the presence of ^{35}S-methionine without further purification (column 7, lines 21-23). In Example 4, mouse L929 fibroblasts are infected with a pro-NGF

vaccinia virus and allowed to express proNGF. The proNGF preparation was then obtained as follows:

> Cells were harvested by scraping, washed in PBS, resuspended iin 50 mM NaCl/100 mM Tris (pH 7.6), and disrupted by sonication, or by two cycles of freezing and thawing. The lysates were cleared of particulate material by centrifugation for 15 min at 4 °C in a microcentrifuge to provide a pro-NGF beta solution. See column 8, lines 1-6; emphases added.

This preparation is clearly not a pharmaceutical composition since it is not usable for administration to an organism in any way. Indeed, it is a crude cell lysate in a buffered solution containing the precursor protein of the "active NGF" and cell debris.

Applicants submit that the above-described crude preparations, if given to a subject, would likely induce a severe immune response, as they contain many components in addition to pro-NGF (e.g., native L929 fibroblast proteins). Thus, none of the pro-NGF-containing preparations described by Edwards can reasonably be considered a pharmaceutical composition (i.e., a composition that can be safely administered to a subject).

The Office Action further states that "[p]harmaceutical compositions are further described in column 10 . . ." See the Office Action, page 4, line 18. Applicants respectfully disagree. The only pharmaceutical composition described by Edwards in column 10 contains β-NGF, not pro-NGF. See column 10, lines 1-22.

Finally, Applicants submit that Edwards provides no suggestion or motivation whatsoever to prepare a proNGF pharmaceutical composition. To the contrary, Edwards states that "[i]t is critical that the final NGF produced be the cleaved, mature hormone because cleavage activates its biological function (R.H. Edwards *et al.* 'Processing of the Native NGF Precursor to Form Biologically Active NGF," in press). See column 5, lines 3-7. Thus, it is clear that the final product taught by Edwards to be useful in a pharmaceutical composition is cleaved proNGF, i.e., β-NGF. In other words, Edwards teaches away from the preparation of a proNGF pharmaceutical composition as recited in amended claim 8.

II

The Office Action speculates that the activity associated with any proNGF is merely due to cellular cleavage of proNGF into β-NGF by target cells, concluding that "cells will naturally

and automatically process the pro-drug, proNGF, into a more active molecule/ingredient" and that "it is immaterial whether proNGF is more active before or after processing by the cell." See page 3, lines 7-10. Applicants submit that this conclusion is contravened by the following three sets of facts:

First, the same type of target cell was used in the activity assays described in the Specification and in Edwards.[1] Thus, the level of cellular conversion of proNGF to β-NGF (by proteolytic cleavage) should have been the same in their assays. Accordingly, if activity associated with proNGF were merely due to its cellular conversion into β-NGF, one would expect the same activity level for Applicants' proNGF and Edwards's proNGF. In fact, however, Applicants' proNGF has substantial activity, but the proNGF disclosed by Edwards has little or no activity. Compare the Specification at, e.g., page 22, line 11 through page 23 line 3 with Edwards at column 9, lines 7-9.

Second, Applicants' proNGF actually has higher activity than β-NGF as demonstrated in two experiments described in a declaration by Dr. Susan Lorey, attached hereto as "Exhibit A." In a first experiment (described in paragraph 2), proNGF is shown to have greater efficacy than β-NGF in inducing embryonic murine fibroblast (3T3 cell line) migration, as compared to the negative control. In a second experiment (described in paragraph 3), proNGF (10^{-6} M) had significantly greater efficacy than β-NGF (10^{-6} M) in inducing bovine epithelial cell migration, as compared to the negative control.

Third, Fahnestock et al. of 2004 (copy of abstract attached hereto as "Exhibit B") and of Nykjaer et al. of 2004 (copy attached hereto as "Exhibit C") provide additional support for the position that proNGF acts independently of β-NGF.

Of note, Fahnestock *et al.* describes that proNGF binds to the high-affinity receptor, TrkA, and "has biological functions beyond its role as a precursor" (emphasis added). Further, Fahnestock states "that proNGF could be responsible for much of the biological activity normally attributed to major NGF in vivo" (emphasis added).

The biological activity of proNGF is explained and clarified in both Fahnestock *et al.* and Nykjaer *et al.* The former reports that proNGF binds to the high-affinity receptor TrkA thereby

[1] Dorsal root ganglion cells were used. See the Specification, page 22, lines 11-29; and Edwards, column 8, lines 54-67.

promoting phosphorylation of TrkA and its downstream signalling effectors. In addition, Nykjaer *et al.* reports that sortilin acts as a receptor of proNGF. It states that "sortilin expression has no impact on NGF responsiveness under these circumstances" (page 847, left column, first paragraph, last sentence) and that "in contrast, mature NGF preferentially binds $p75^{NTR}$ and/or TrkA, with sortilin having little or no bearing on NGF-initiated signalling" (page 847, left column, second paragraph).

Thus, contrary to the assumption in the Office Action that β-NGF is the sole active compound, i.e., attributing the biological activity of proNGF to its digested form, experts in the growth factor field even suspect that much of the biological activity previously attributed to NGF is actually due to proNGF activity. It is quite telling that the just-discussed scientific reports were both published six years after the instant invention was made.

In view of the above remarks, Applicants submit that the activity of proNGF is not explicable by its cellular conversion into β-NGF as asserted in the Office Action. Rather, proNGF acts independently of β-NGF.

Thus, the Office Action's allegation that "Edwards ... only supports the argument that cells will naturally and automatically process the pro-drug, proNGF, into a more active molecule/ingredient" has been successfully traversed, considering the present application and the recent scientific literature.

III

In view of the foregoing analysis, Applicants submit that claim 8 is not anticipated by Edwards. Applicants further submit that for at least the same reasons, claim 20, dependent from claim 8, is also not anticipated by Edwards. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Based on the remarks set forth above, Applicants submit that the pending claims cover allowable subject matter. Allowance by the Examiner is respectfully solicited.

Enclosed is a Petition for Three Month Extension of Time, with the required fee of $510. Please apply any other charges to deposit account 06-1050, referencing attorney docket. 13028-002001.

Respectfully submitted,

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